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REVIEW ARTICLE

Genetic defects of ovarian TGF-β-like factors and premature ovarian failure

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ABSTRACT. Premature ovarian failure (POF) is an ovarian defect characterized by the premature depletion of ovarian follicles; POF affects approximately 1-2% of women under the age of 40 yr, thus representing one major cause of female infertility. POF relevance is continuously growing because women tend to conceive always more frequently beyond 30 yr. Frequently, POF is the end-stage of an occult process [primary ovarian insufficiency (POI)]. POI is a heterogeneous disease caused by a variety of mechanisms. Though the underlying cause remains unexplained in the majority of cases, several data indicate that POI has a strong genetic component. These data include the existence of several causal genetic defects in human, experimental, and natural models, as well as the frequent familiarity. The candidate genes are numerous, but POF remains unexplained in most of the cases. Several recent evidences have driven the attention of researchers on the possible involvement of various elements belonging to the transforming growth factor β family, which includes bone morphogenetic proteins, growth/differentiation factors, and inhibins. These peptides are produced by either the oocyte or granulosa cells to constitute a complex paracrine network within the ovarian follicle. Here, we review the studies reporting the genetic alterations of these factors in human and animal defects of ovarian folliculogenesis which support the fundamental roles played by these signals in ovarian morphogenesis and function.
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INTRODUCTION

Approximately 1% of women under the age of 40 yr and 0.1% under the age of 30 yr experience premature menopause (1). Premature ovarian failure (POF) is classically defined as 4-6 months of amenorrhea in women under the age of 40 yr associated with menopausal level of serum gonadotropins (FSH>30 U/l) and hypoestrogenism and is also referred to as hypergonadotropic hypogonadism. Depending on the age of onset, the disorder can manifest as primary amenorrhea (PA), without menarche, or secondary amenorrhea (SA) after the pubertal development (2). Based on evidence that POF may have a long and variable clinical course, it has been recently proposed the term of primary ovarian insufficiency (POI), as a more scientifically accurate definition, to better describe the progression towards the cessation of the ovarian function (3, 4). POI generates a premature hypoestrogenic state which in turn causes the premature aging of several tissues, targets of estrogen action, thus increasing the risk of osteoporosis, cardiovascular or neurodegenerative diseases. Hypoestrogenism can nowadays be satisfactorily treated by hormone replacement therapy to be generally given until the age of physiological menopause. Importantly, POF also causes infertility, but fertility cannot be recovered when the diagnosis of POF (or end-stage POI) is generally reached, and is often compromised in the early phases of the disease when the clinical manifestations are absent. For this reason, the research in this field aims at the identification of markers able to predict the premature cessation of menses, thus allowing women at risk of POF to program an early conception. Biochemical markers (FSH, estradiol, inhibin B or anti-mullerian hormone) are nowadays mainly useful to confirm a diagnosis indicated by menstrual irregularity. Prediction of POI therefore relies on a better understanding of its pathogenesis.

MECHANISMS LEADING TO OVARIAN INSUFFICIENCY

Around 7 millions of primordial follicles are present in the developing ovary during embryogenesis. The large majority of these follicles are lost during fetal and post-natal life by atresia and only 400-500 of them are generally ovulated (<1 out of 14,000 primordial follicles) before physiological menopause. Instead, ovarian insufficiency can be the consequence of many different pathological conditions affecting the physiological folliculogenesis at various levels and the possible mechanisms at the origin of POI can be: a) a diminished size of the primordial follicle pool; b) an accelerated follicular atresia; or c) an altered recruitment of primordial follicles. However, in most of the cases, including some forms of primary amenorrhea and gonadal dysgenesis (5, 6), ovarian insufficiency occurs because of an anticipated depletion of the primordial follicular pool. The etiological causes that may

Key-words: BMP15, female reproduction, folliculogenesis, GDF9, menopause, oocyte, ovary, premature ovarian failure (POF), primary ovarian insufficiency (POI).

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activate such mechanisms are highly heterogeneous and include chromosomal, genetic, autoimmune, metabolic, infectious, and iatrogenic factors (7). At present, 25-30% of all forms of POF can be classified as iatrogenic and related to cancer treatment, but >50% of the cases remain idiopathic, so that the origin of POI is still largely unknown.

The age of menopause is largely determined by inheritable factors (8, 9). In particular, familiar forms of POF constitute about $^1/_3$ of total idiopathic cases, thus suggesting the existence of a relevant genetic component in the pathogenesis of this disease (10-12). Understanding these genetic mechanisms would then allow the generation of predictive tests for the prediction of menopausal age. Recent insights into the mechanisms regulating ovarian folliculogenesis revealed the relevant role played by several elements of the transforming growth factor-β (TGF-β) family. Here below, we illustrate the findings supporting the involvement of some of these factors in the genetic predisposition of human and animal ovarian defects.

THE TGF-β FAMILY

TGF-β belong to the superfamily of cysteine-knot growth factors which also include the glycoprotein hormone family [LH, chorionic gonadotropin hormone (CG), FSH, TSH], the platelet-derived-growth factor (PDGF) family and the neurotrophin family (including the nerve growth factor) (13). The TGF-β family of growth factors and receptors is constituted by the bone morphogenetic protein (BMP) system, along with growth and differentiation factors (GDF), activin/inhibin peptides, anti-mullerian hormone (AMH), and the myostatin protein. These factors act through 2 subtypes of single transmembrane domain receptors with serine-threonine kinase activity. In particular, Alk-2, 3, and 6 act as type 1 receptors for BMP factors, whereas BMP receptor-2 (BMPR-2), activin receptor-2 and 2B (ActR-2, ActR-2B) are type 2 receptors. All these proteins promote growth and differentiation in the target tissues since the early stages of embryonic development and are generally involved in paracrine actions also in adult tissues. TGF-β are commonly translated as pre-pro-proteins (14). The pro-region typically regulates post-translational processing and dimerization of mature peptide forming either hetero- or homo-dimeric proteins which finally exert the biological activity at the target cell (Fig. 1). In order to achieve this, dimeric BMP molecules interact with heterotetrameric complexes of type 1 and type 2 receptors. Within each complex, the constitutive kinase activity of the type 2 receptor phosphorylates the type 1 receptor. Once phosphorylated, the type 1 receptor recruits and phosphorylates intracellular signaling molecules of the Smad proteins family. The phosphorylated BMP receptor-regulated Smads (Smad 1, 5 or 8) interact with the common Smad 4 and translocate to the nucleus where these hetero-complexes act as transcriptional factors or co-factors to regulate target genes expression (14).

Several members of the TGF-β family are expressed in the ovarian follicle, either by the oocyte or by granulosa cells (GC) (15). Among the proteins involved in these signals within the ovary, the association between genetic variations and defects of human folliculogenesis have been so far described for the ligands BMP15, GDF9, and INHA as well as for the receptor BMPR-IB (Table 1).

BONE MORPHOGENETIC PROTEIN 15

BMP15 gene (also named *GDF9b*; MIM *300247) encodes for an oocyte-derived growth and differentiation factor which is involved in follicular development as a critical regulator of many GC processes (14-17) (Fig. 2).

The relevance of BMP15 action in ovarian folliculogenesis was initially shown by experimental and natural models. Experimental disruption of *Bmp15* gene in mice caus-

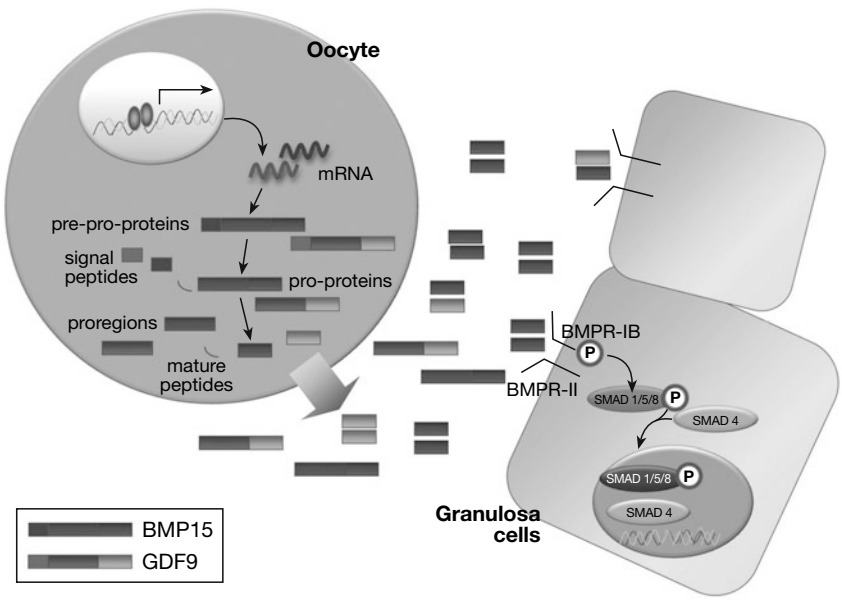

Fig. 1 - *Schematic illustration of the synthesis of bone morphogenetic protein (BMP) 15 and growth and differentiation factors (GDF) 9 in ovarian follicles. The factors are synthesized as pre-pro-proteins that are processed to produce the mature proteins. Either precursors and mature proteins can be secreted in the follicular fluids. Mature proteins are assembled as homo- or hetero-dimers, which exerts the biological activities (i.e., stimulation of growth, anti-apoptotic effects or regulation of differentiation and FSH receptor expression) on the GC. The intracellular signals in chorionic gonadotropin hormone (CG) are generated by the dimerization of BMP receptors type I and II (BMPR-I, BMPR-II. The consequent phosphorylation of BMPR-IB, in this case, activates downstream pathways affecting transc-ription.*

Table 1 - *Genetic alterations of different elements of bone morphogenetic protein (BMP)/growth and differentiation factors (GDF) signal and their effects on ovarian folliculogenesis in human and animal models.*

	BMP15 (MIM *300247)	GDF9 (MIM *601918)	INHA (MIM *147380)	BMPR-IB (MIM *609441)
Human	Heterozygous missense variants in 1.5-15% of idiopathic POF Homozygous nonsense deletion in one girl with ovarian dysgenesis, facial paralysis and skewed lower mandible No association with PCOS or dizygotic twinning	Heterozygous missense variants in 1.4% of idiopathic POF Significant association with dizygotic twinning No association with PCOS	Heterozygous missense variant in 0-11% of idiopathic POF	Homozygous deletion in Demirhan syndrome (acrosomelic chondrodysplasia, ovarian dysgenesis)
Knock-out mice	Female-limited subfertility in homozygotes	Female-limited infertility and ovarian dysgenesis in homozygotes	Sex chord stromal tumors, adrenal steroidogenic cell tumors, block of folliculogenesis in homozygotes	Brachydactyly and infertility in female homozygotes (due to cumulus expansion and post-ovulatory defects)
Sheep	Increased ovulation rate (+++)[a] in heterozygotes (FecX: missense variants) Sterility and block of folliculogenesis (primary stage) in homozygotes[b]	Increased ovulation rate (++)[a] in heterozygotes (FecG: missense variants) Sterility and block of folliculogenesis (antral stage) in homozygotes[b]	----	Increased ovulation rate in heterozygous (+)[a] and in homozygous (++++)[a] carriers (FecB: missense variant)

[a]The number of + indicates the grading of increased ovulation rate. [b]Recent data show increased ovulation rates in homozygous carriers of BMP15 (FecX) or GDF9 (FecG) variants in Moghani and Ghezel (28) or Santa Ines (48) sheep. Only double FecX/FecG homozygotes would be sterile (28).

es a mild fertility defect limited to females (18), whereas natural missense mutations in several strains of ewes cause a hyperprolificacy phenotype in the heterozygous state (increased litter size to 2-5 lambs per litter against 1 in wild-type) and a female infertility with complete block of folliculogenesis in the homozygous state (FecX factors) (19-23) (Table 1). Nowadays, the BMP15 main roles include: a) the promotion of follicle maturation since the primordial gonadotropin-independent phases of folliculogenesis; b) regulation of follicular GC sensitivity to FSH action; c) prevention of GC apoptosis; d) promotion of oocyte developmental competence; e) regulation of ovulation quota (15) (24-27) (Fig. 2). The mutations found in sheep generally occur in the mature peptide and lead to a diminished protein production and should thus be considered as loss-of-function. The reduced BMP signal generated by the mutation would then favor the formation of smaller primary/pre-antral follicles with a lesser amount of GC that are more sensitive to FSH stimulation. This would finally lead to the hyperprolificacy phenotype with increased ovulation rate and litter size. The block of folliculogenesis observed in the homozygous sheep was instead interpreted as the result of a critical gene dosage effect in which the lack of BMP15 signal would then be incompatible with the progression of folliculogenesis (24). However, the redundancy between the oocyte-derived

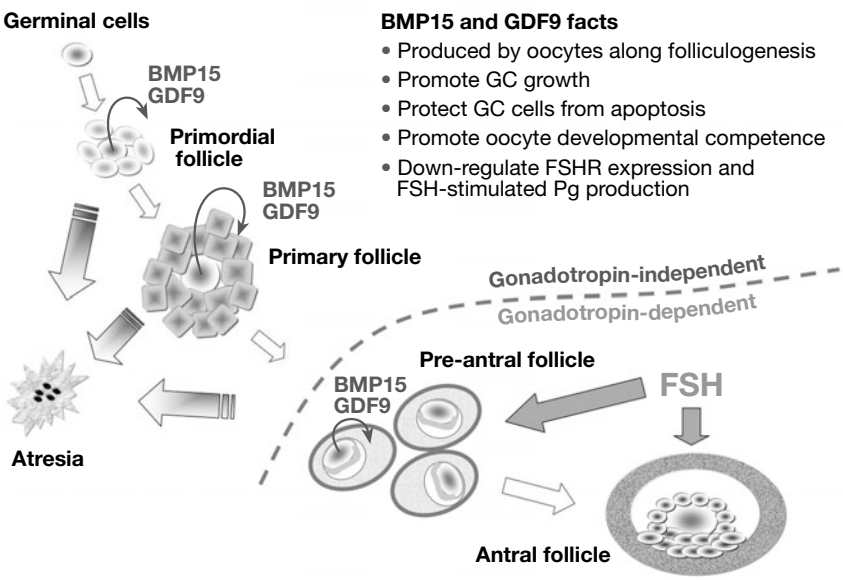

Fig. 2 - *Schematic representation of the ovarian folliculogenesis. Both bone morphogenetic protein (BMP) 15 and growth and differentiation factors (GDF) 9 are produced all along the process by the oocyte and contribute to the generation, growth and maturation of the follicle. Their activity is strictly connected to the FSH sensitivity of chorionic gonadotropin hormone (CG). FSHR: FSH receptor.*

BMP15 and GDF9 was difficult to reconcile with this interpretation. Very recent data (28) indicate that the co-existence of BMP15 and GDF9 inactivation would then be required for the infertility phenotype in ewes.

BMP15 maps to a locus on the short arm of X chromosome (Xp11.2) within a "POF critical region" where are located several of the Turner syndrome traits including ovarian failure (29, 30). In humans, mutations in *BMP15* gene have been found in association with both primary and secondary amenorrhea in several worldwide POI cohorts with a variable prevalence between 1.5-15% (Table 2). The first heterozygous mutation of *BMP15* gene (p.Y235C) was reported by us in 2 Italian sisters with primary amenorrhea and ovarian dysgenesis, who inherited the genetic alteration from the unaffected father (31). This mutation was located in a residue highly conserved among species and generated aberrant high molecular weight products *in vitro* as seen at western-blot in non-reducing conditions, a likely consequence of the additional Cys in the pro-region. A bioassay on primary cultures of human GC showed an impairment of the growth stimulatory activity of recombinant mutant BMP15 in comparison with wild-type protein. Co-incubation experiments of wild-type and p.Y235C proteins were consistent with a dominant negative effect (DNE) exerted by the mutant on the stimulatory activity of wild-type protein on GC (31). Afterwards, other variants have been identified with variable frequency in patients from Europe, USA, North Africa, India, China, and other Asian countries (32-38) (Table 2). Almost all of these are missense variations found in the heterozygous state. These variations are also located in the gene sequence encoding the pro-region of the protein. More recently, we studied the recombinant products of several of these missense variations and showed an impaired amount of mature BMP15 protein produced by variant vectors in comparison with wild-type, suggesting a hampered processing. Consistently, we showed a significant reduction of their biological effects by using a novel BMP-responsive luciferase-reporter assay on a human granulosa cell line (36). Co-transfection of equal amounts of wild-type plasmids failed to completely restore the normal transcriptional activity. Since a reduced production of bioactive proteins was seen at western-blot, we interpreted these results as consistent with a mechanism of haploinsufficiency similar to that described for the mutations found in sheep. Among all the identified variations, only one was found to cause a premature truncation. This truncated variant creates a premature stop in the pro-region (p.E211X), resulting in the complete lack of mature BMP15 peptide, and was found in an Indian woman with PA and ovarian dysgenesis (34). Very recently, a Chinese group reported the first missense substitution (p.R329C) located in the region of the mature peptide that, involving an Arg to Cys aminoacidic change, could alter the structure of BMP15 by impairing the correct folding of the protein (37). This variant co-segragated with POF phenotype in mother and daughter. To date, only two studies failed to find an association between BMP15 mutations and POI: a Japanese group (39) and a group from New Zealand (40) which reported the absence of BMP15 mutations in series of women with SA. One possible explanation for these negative results may be represented by the small size of the cohorts studied (15 and 38 POF patients, respectively). Importantly, some of the missense variations in *BMP15* gene have also been found in low percentage in the control populations (see Table 2 for details), a finding that may question or diminish their pathogenic role. In light of these findings, one could hypothesize that BMP15 variations might play a predisposing role in a context of POI considered as a complex multifactorial disorder, in contrast with the view of POI as a monogenic disorder. However, before drawing conclusions, it must be emphasized that the correct control population of these studies should be represented by women of the same ethnicity and with proven physiological menopause beyond the age of 50 yr. Unfortunately, both these conditions were not met in most of the studies reporting BMP15 variants, as were instead

Table 2 - *Frequency of bone morphogenetic protein (BMP) 15 and growth and differentiation factors (GDF) 9 non-synonimous variants in patients with primary ovarian insufficiency (POI) and controls of different ethnicity.*

Origin	Size of POI cohort	Patients with BMP15 variations	Patients with GDF9 variations	Size of contol population (% of carriers)	Reference
Japan	15	0%	0%	----	39
New Zealand	38	0%	0%	51 (0%)	40
Europe & USA (Caucasian)	166	4.2%*	----	211 (0%)*	32
Europe & North Africa	203	1.5%*	0.5%	54 (0%)*	33
India	195	----	3.6%	220 (0%)	50
India	202	8.9%*	----	197 (0%)*	34
USA (mixed ethnicities)	61	----	1.6%	60 (0%)	51
Germany	20	15%*	0%	127 (BMP15: 0.8%; GDF9: 0%)*	35
Italy & USA (Caucasian)	300	4.3%*	----	216 (0%)*	36
China	100	6%*	0%	100 (BMP15: 1%; GDF9: 0%)*	37
Europe, North Africa & Asia	50	12%*	----	214 (1.9%)*	38

*After exclusion of BMP15 p. ins263L, p.N103S variants that were found in 3-12% of POI patients and controls.

in the studies designed by our group (32, 36).
The functional mechanism by which BMP15 variants with a proved biological impact may disturb human ovarian folliculogenesis is presently unknown. We may envisage that a diminished BMP15 paracrine signal in the follicle would involve an impairment of the anti-apoptotic effects on GC, a mechanism then favoring follicle atresia. Alternatively, BMP15 variants may finally result in an altered recruitment of pre-antral follicles by gonadotropins. For this reason, *BMP15* gene has also been investigated in patients with different ovulation alterations, and no linkage was found either in patients with polycystic ovaries (PCOS) and in mothers with spontaneous dizygotic twinning (41, 42). Indeed, further studies are needed to understand the exact role of BMP15 variants in POI pathogenesis. Interestingly, all the findings here described for several human variants might also suggest *BMP15* as the first X-linked gene whose haploinsufficiency may play a determinant role for the generation of ovarian dysgenesis in Turner syndrome (43-45).
All together, the data so far collected in different mammalian species indicate that the role of BMP15 may be more critical in mono-ovulating species (such as human and sheep) than in the poly-ovulating ones (mice). Indeed, it appears that in the mono-ovulating human species, 2 functional copies of *BMP15* are required, since the presence of a heterozygous mutation is sufficient for POF. In ovine species, BMP15 loss of function is associated with a large ovulation rate ranging. Finally, in a poly-ovulating species such as the mouse, with ovulation rate about 10, BMP15 appears dispensable. However, BMP15 is present and expressed in oocytes of these 3 species. As a possible explicative mechanism, Hashimoto et al. (27) have shown that the mouse BMP15 peptide is much less efficiently processed and secreted than the human peptide by the same transfected cells.

GROWTH DIFFERENTIATION FACTOR 9

Growth differentiation factor 9 (*GDF9*) (MIM *601918) is the homologous gene of *BMP15* and is also expressed in the oocyte. Its product can form non-covalent heterodimers acting in a synergistic manner on ovarian function on surrounding follicular GC (18). From experimental animals, GDF9 function is more critical in poly-ovulating species such as mice where GDF9 is required for folliculogenesis (46). Natural *GDF9* gene mutations with ovarian effects similar to those seen in BMP15 mutants were also detected in Cambridge, Belclare, and Thoka sheeps (21, 47). More recently, a new missense mutations was found in the Brazilian Santa Ines breed (48). In contrast with previous observations, the fecundity phenotype was present either in heterozygous and homozygous sheep (see BMP15 section for the interpretation of these findings) (Table 1). GDF9 was shown *in vitro* to stimulate cumulus expansion, with the induction of hyaluronan synthase 2 (HAS2), cyclooxygenase 2 (COX2), and steroidogenic acute regulator protein (StAR) (49). As BMP15, GDF 9 was also shown to reduce the sensitivity of GC to FSH action and to inhibit the FSH-stimulated progesterone and estradiol production (24).
On all these bases, *GDF9* was therefore considered a candidate gene for human POI. The first mutational screening of the *GDF9* gene was reported in 15 Japanese women with premature ovarian insufficiency, but no mutations were found (39). Following this first study, a more extensive number of POI patients (no.=629) have been screened for mutations in the coding region of *GDF9* gene (Table 2). GDF9 human variations described so far in different ethnicity (p.K67E; p.V216M; p.S186Y; p.P103S and p.T238A) are all heterozygous, affect exclusively the proregion with a prevalence of 1.4% and were not detected in the control samples (33, 50-52). Some studies, however, failed to identify possible deleterious variants suggesting a rare contribution of *GDF9* gene variations in those populations (37, 40). Some rare insertion/deletion and missense variations in *GDF9* gene have been also associated with spontaneous dizygotic twinning, the reported frequency of these variants is around 4% confirming a possible role of this factor in the determination of ovulation quota also in humans (53-55). No association was instead found with PCOS (41). However, the expression of GDF9 mRNA, but not that of BMP15, was found delayed and reduced in the oocytes of PCOS women during their growth and differentiation phase (56). These results may suggest that a dysregulation of oocyte GDF9 expression may contribute to the aberrant folliculogenesis in PCOS.

INHIBIN A

Inhibin is another candidate gene for mutational studies in humans, given its important role in regulating ovarian function either as negative modulator of pituitary FSH synthesis or as a paracrine factor. Inhibin A (inhA) gene knock-out (KO) mice lack the bioactive inhibin dimers thus resulting in raised FSH levels, infertility, and sex chord stromal tumors at an early age with nearly 100% penetrance, demonstrating that inhibin functions *in vivo* as a tumor suppressor in the gonads of mice (57). In a subsequent work, Matzuk et al. (58) showed that inhA-KO mice eventually developed adrenal cortical sex steroidogenic tumors with nearly 100% penetrance, demonstrating that inhibin is also a tumor suppressor for the adrenal gland. The first evidence of a genetic association between inhibin and POI came forth from a POI patient with the traslocation 46,XX,t(2;15)(q32.3;q13.3). The translocation breakpoint on chromosome 2 interested the inhibin α (*INHA*) (MIM *147380) subunit locus (2q33-36), therefore further investigations have been aimed at the mutational screening of this gene (59). One missense variation of *INHA* gene (p.A257T) has been associated with POI in several populations (60-62), with a prevalence of 0-11% depending on the ethnicity of the population studied. In fact, the highest frequency of INHA variant was found in the Indian population (62, 63) and in the New Zealand study, including also Slovenian patients (60). An Italian study reported a significant association between the INHA p.A257T variant and sporadic (4.5%) and familial POI cases (7.7%) (61). However, the study has been recently replicated in a larger cohort of Italian and German subjects and no differences in variant frequency were detected between POI cases and controls (64). The *INHA* variation is also rare in populations from Argentina (65) and Korea (66). Nevertheless, a

recent meta-analysis of the random effects on the risk of POI in carriers of the *INHA* variant from the most relevant studies revealed a combined risk difference of 0.04 (–0.03 to 0.11) with 95% confidence interval (67). On these bases, it is plausible that the *INHA* variant allele might confer a susceptibility to develop POI. This view may also be confirmed by the functional study demonstrating a reduced bioactivity of INHA variant in the inhibition of an inhibin-reporter in mouse LβT2 pituitary gonadotrope cells, whilst variable results were seen when the reporter was expressed in COV434 granulosa cell line; interestingly dimerization with β-subunits was unaffected by the variation (68). Moreover, 2 promoter variations (c.-16C>T and c.-124A>G) were also reported as additional mechanisms potentially affecting the transcriptional regulation of *INHA* gene and predisposing to POI. However, the association with POI never reached the statistical significance in all the populations studied (61, 64, 69, 70). In humans, no variations were ever found in the inhibin βA or βB subunit.

BMP RECEPTOR IB

Demirhan et al. (71) reported the case of a 16-yr-old girl with acromesomelic chondrodysplasia, genital anomalies, amenorrhea, and hypergonadotrophic hypogonadism due to a homozygous variant of BMP receptor IB (*BMPRIB*) gene (also named Activin receptor-Like Kinase 6 or ALK6; MIM *609441). Acrosomelic chondrodysplasias are hereditary skeletal disorders characterised by short stature, very short limbs and hand/foot malformations. They are caused by homozygous mutations in growth differentiation factor 5 (GDF5), a bone morphogenetic protein (BMP) belonging to the TGF-β superfamily which binds to *BMPRIB* with high affinity, and plays an essential role in chondrocyte differerentiation (72). The skeletal phenotype of the patient with *BMPRIB* mutation is similar to that observed in patients with homozygous variations of *GDF5* gene, who instead do not have gonadal defects. Mutation analysis of *BMPRIB* revealed a homozygous 8 bp deletion (del359-366). This mutation is expected to result in a loss of function and is thus different from the heterozygous missense mutations in BMPRIB recently shown to cause brachydactyly type A2 through a dominant negative effect (73). *BMPRIB* variants can occur naturally also in animals and are found associated with the hyperproliphic Booroola phenotype in sheep (74, 75), while the female KO mice present with brachydactyly and infertility (76). Interestingly, the natural mutation has additive effects on ovulation rate and fecundity in sheep (Table 1). These findings highlight the dual function of BMPRIB: on one hand in skeletal development as the predominant receptor for GDF5 and, on the other, its role in genital development and ovarian function. Since BMPR-IB is expressed in GC, it is considered the putative type 1 receptor for oocyte-derived BMP and GDF (Fig. 1).

CONCLUSIONS

Until 10 to 15 yr ago, two major systems were known to contribute to the regulation of ovarian function, ie. gonadotropins or IGF systems. In recent years, with the identification of the nature and the physiological role of fecundity genes, such as BMP15, GDF9, and BMPRIB, and of other ovarian TGF-β, such as inhibins, several new major concepts were generated. First, the BMP system, originally described as inducer of osteogenesis and chondrogenesis and implicated in early developmental events, now represents also a key system in the control of ovarian folliculogenesis and ovulation rate. Second, the oocyte, acting through specific secreted proteins, is not only implicated in follicular growth but also in the control of folliculogenesis and of the number of ovulating follicles (17). On the other hand, TGF-β-related factors produced by GC, such as inhibins, contribute to the generation of a paracrine and endocrine network playing a fundamental part in the regulation of female fertility. These new concepts have therefore engendered revolutionary insights into the understanding of ovarian folliculogenesis.

Several BMP and GDF are expressed by the oocyte and GC possibly suggesting redundancy of these signals that are so relevant for reproduction. On this line, the heterozygous inactivating variations here described would play a predisposing role in the pathogenesis of POF and not a direct causative mechanism, as seen in classic monogenic diseases. This interpretation is consistent with the idea that POF may be considered a complex disease, probably involving defects in multiple genes (77). In an order of association frequency with idiopathic POF, BMP15 variations appear as the second defect, behind FMR1 premutation (78). However, all these novel candidates appear involved in the predisposition of a limited percentage of POF cases (<10%) and other fundamental mechanisms are still to be identified. Novel insights could be given by a more intimate understanding of the molecular mechanisms elicited by the oocyte BMP in the target GC.

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Disclosure statement

The Authors have nothing to disclose related to this work.

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